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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/951,188	10/15/1997	DAVID H. PRICE	IOWA-012/FUS	1309
23720	7590	03/19/2004	EXAMINER	
WILLIAMS, MORGAN & AMERSON, P.C. 10333 RICHMOND, SUITE 1100 HOUSTON, TX 77042			STEADMAN, DAVID J	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 03/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

08/951,188

Applicant(s)

PRICE, DAVID H.

Examiner

David J Steadman

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 January 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) See Continuation Sheet is/are rejected.
- 7) ☒ Claim(s) 112,130-132,144-146,154-156,170,171,174-176 and 184 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] In view of the new rejections as set forth in the instant Office action, the finality of the rejection of the Office action mailed September 09, 2003 is withdrawn.

[2] Claims 110-113, 116-164, 167-172, 174-184, 186-189, 191-193, 195-208, and 211-218 are pending in the application.

[3] Applicants' amendment to the claims filed January 12, 2004 is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Applicants' arguments filed on January 12, 2004 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Specification/Informalities

[6] The use of the trademarks "Centricon-30", "Mono S", and "Phenyl Sepharose" has been noted in this application (see, e.g., page 137). They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

[7] Claims 140-143, 164, 167-172, 174-177, 204-208, 211-216 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n).

[8] Claim 151 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. It is suggested that, for example, the claim is amended to depend from claim 149.

Claim Rejections - 35 USC § 112, Second Paragraph

[9] Claims 125-127, 172, and 177 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 125-127, 172, 177 recite the limitation "SEQ ID NO:50". There is insufficient antecedent basis for this limitation in the claims. In order to correct antecedent basis, it is suggested that, for example, applicant amend the claims to be dependent upon claim 113.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

[10] Claims 113, 116-127, 158-162 and 218 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to nucleic acid fragments or one or more expression units. The claims read on a product of nature and should be amended to indicate the hand of the inventor, e.g., by insertion of "purified" or "isolated". See MPEP § 2105.

Claim Rejections - 35 USC § 112, First Paragraph

[11] Claim 133 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 133 is drawn to a genus of isolated nucleic acid molecules comprising a nucleic acid fragment and a promoter. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

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MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. With respect to the genus of nucleic acids of claim 133, the specification discloses only a SINGLE representative species of the claimed genus of nucleic acids, i.e., an isolated nucleic acid molecule consisting of the nucleic acid fragment (as set forth in claim 113) and a promoter. Other than this SINGLE disclosed species, the specification fails to describe any additional representative species of the claimed genus. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". In the instant case, the claimed genus of nucleic acid molecules encompasses species that are widely variant in both structure and function, including (but not limited to) genomic sequences, allelic variants, and nucleic acid variants encoding polypeptides having function other than the asserted kinase activity, e.g., non-functional polypeptides. As such, the disclosure of the single representative species as described above is insufficient to be representative of the attributes and features of all species encompassed by the claimed genus of nucleic acid molecules. Given the lack of description of a representative number of polynucleotides, the specification fails to sufficiently describe the claimed invention in such full, clear,

concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

It is noted that claim 133 was previously rejected under 35 USC 112, first paragraph, for a lack of written description (see item [12] of the Office action mailed March 10, 2003), which was subsequently withdrawn in the Office action mailed September 09, 2003. However, upon further consideration of the claim, the examiner has reinstated the rejection for those reasons stated above.

[12] Claim(s) 133, 136-143, 149-153, 157-164, 167-168, 177-183, 186-189, 191-193, 195-202, 205-208, and 211-218 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid fragment of an isolated nucleic acid consisting of a nucleotide sequence encoding SEQ ID NO:4, 45, 47, and 50, does not reasonably provide enablement for all isolated nucleic acids comprising a fragment of a nucleic acid consisting of a nucleotide sequence encoding SEQ ID NO:4, 45, 47, and 50 and fusions thereof (relevant to claims 133 and 136). Also, the specification, while being enabling for an isolated nucleic acid molecule encoding SEQ ID NO:2, 4, 6, 45, 47, and 50, does not reasonably provide enablement for all isolated nucleic acid molecules encoding variants of SEQ ID NO:2, 4, 6, 45, 47, and 50 as encompassed by claims 137-143, 149-153, 157-164, 167-168, 177-183, 186-189, 191-193, 195-202, 205-208, and 211-218. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to encompass all isolated nucleic acids comprising a fragment of a nucleic acid encoding SEQ ID NO:4, 45, 47, and 50 and fusions thereof (relevant to claims 133 and 136) and all isolated nucleic acid molecules encoding variants of SEQ ID NO:2, 4, 6, 45, 47, and 50 as encompassed by claims 137-143, 149-153, 157-164, 167-168, 177-183, 186-189, 191-193, 195-202, 205-208, and 211-218. The broad scope of claimed nucleic acids is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of nucleic acids broadly encompassed by the claims. In this case the disclosure is limited to an isolated nucleic acid fragment of an isolated nucleic acid consisting of a nucleotide sequence encoding SEQ ID NO:4, 45, 47, and 50 or an isolated nucleic acid molecule encoding SEQ ID NO:2, 4, 6, 45, 47, and 50.

- The lack of guidance and working examples: The specification provides the following working examples of the claimed nucleic acids: SEQ ID NO:1, 3, 43, 44, 46, 48, and 49. These working examples fail to provide the necessary guidance for making the entire scope of claimed nucleic acids and, thus the specification fails to provide guidance for altering the sequences by substitution, deletion or insertion with an expectation of maintaining the desired activity.
- The high level of unpredictability in the art: The encoding nucleic acid sequence determines an encoded protein's structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained above. Thus, a skilled artisan would recognize the high level of unpredictability in making the entire scope of claimed polynucleotides with an expectation that the encoded polypeptides will have the desired activities.

- The state of the prior art supports the high level of unpredictability: The state of the art provides evidence for the high degree of unpredictability in altering the amino acid sequence of a polypeptide with an expectation that the polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). While it is acknowledged that this reference was published in 1991, to date there remains no certain method for reasonably predicting the effects of even a *single* amino acid mutation on a protein.
- The amount of experimentation required is undue: While methods of isolating variants of a protein-encoding sequence are known, e.g., by site-directed mutagenesis or hybridization, it is not routine in the art to screen for all nucleic acids having a substantial number of modifications, as encompassed by the instant claims. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated

with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

It is noted that a scope of enablement rejection under 35 USC 112, first paragraph, was raised in a previous Office action (see item [13] of the Office action mailed March 10, 2003), which was subsequently withdrawn in the Office action mailed September 09, 2003. However, upon further consideration of the scope of claimed nucleic acids, the examiner has reinstated the rejection for those reasons stated above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

[13] Claim(s) 110-111, 113, 116-129, 133-137, 147-149, 152, 157-161, 164, 167-169, 178-181, 183, 186, 195-201, 203-208, 211-213, 215-218 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marshall et al. (*J Biol Chem* 270:12335-12338; cited as reference C38 in the IDS filed April 20, 1998) in view of Matsudaira

(*Methods Enzymol* 182:602-613), Wozney (*Methods Enzymol* 182:738-751), and Ausubel et al. ("Current Protocols in Molecular Biology", John Wiley and Sons, Inc., New York, 1997). The claims are drawn to (in relevant part) nucleic acids encoding SEQ ID NO:2 and/or 4 and host cells comprising said encoding nucleic acids.

Marshall et al. teach a method for the purification of Drosophila P-TEFb (page 12336, left column), yielding a polypeptide with two subunits having MWs of 124 and 43 kDa (page 12337, left column). Marshall et al. teach that further characterization of P-TEFb is desired, in particular to define the P-TEFb mechanism of action (page 12338, right column). Marshall et al. do not teach the corresponding nucleic acids encoding the subunits of Drosophila P-TEFb.

At the time of the invention, the skill of one of ordinary skill in the art was such that the artisan could use conventional techniques to: 1) obtain a partial amino acid sequence of a purified polypeptide; 2) synthesize a degenerate polynucleotide probe based on the partial amino acid sequence; 3) use the polynucleotide probe to screen a cDNA or genomic library and identify a full length cDNA or genomic clone; 4) construct expression vectors comprising the isolated cDNA or genomic clone; 5) transform a host cell with an expression vector comprising the isolated cDNA or genomic clone and 6) express the encoded polypeptide using the transformed host cell. As evidence of the state of the art at the time of the invention, Matsudaira teaches methods for the determination of N-terminal amino acid sequences (see pages 602-604), and Wozney teaches methods of using a purified protein to clone the corresponding encoding nucleic acid for expression of the encoded protein using a recombinant host cell (page 738).

Wozney teaches the considerations for the selection of peptide candidates for the production of degenerate oligonucleotide probes, synthesis of oligonucleotide probes, screening of genomic or cDNA libraries, and isolation and amplification of cDNA or genomic clones (pages 738-751).

Also, at the time of the invention, methods of inserting nucleic acids into expression vectors and expressing a eukaryotic protein using a bacterial or mammalian cell were well known in the art. For example, Ausubel et al. teach various methods of expressing proteins, including fusion proteins, using prokaryotic and eukaryotic host cells comprising expression vectors encoding said proteins.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Marshall et al., Matsudaira, Wozney, and Ausubel et al. to isolate nucleic acids encoding the subunits of P-TEFb, insert said nucleic acids in an expression vector and to recombinantly express the encoded proteins. One would have been motivated to recombinantly express P-TEFb in order to generate a relatively larger amount of protein (than can be obtained non-recombinantly) in order to further characterize P-TEFb as suggested by Marshall et al. One would have a reasonable expectation of success for isolating the nucleic acids encoding the subunits of P-TEFb, inserting said nucleic acids in an expression vector and recombinantly expressing the encoded proteins because of the results of Marshall et al., Matsudaira, Wozney, and Ausubel et al. Therefore, claims 110-111, 113, 116-129, 133-137, 147-149, 152, 157-161, 164, 167-169, 178-181, 183, 186, 195-201, 203-208, 211-213, 215-218, drawn to

nucleic acids and host cells as described above would have been obvious to one of ordinary skill in the art at the time of the invention.

It is noted that the instant application was transferred from Examiner Tung to Examiner Steadman. In light of MPEP 704.01, Examiner Tung's prior art search was given full faith and credit. However, in view of the prior art cited in the rejection stated above, it is the examiner's position that the claimed invention would have been obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

[14] Status of the claims:

- Claims 110-113, 116-164, 167-172, 174-184, 186-189, 191-193, 195-208, and 211-218 are pending.
- Claims 110-111, 113, 116-129, 133-143, 147-153, 157-164, 167-169, 172, 177-183, 186-189, 191-193, 195-208, and 211-218 are rejected.
- Claims 112, 130-132, 144-146, 154-156, 170-171, 174-176, and 184 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or

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informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.

Patent Examiner

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[Signature] 03-17-04

Continuation Sheet (PTOL-326)

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Continuation of Disposition of Claims: Claims pending in the application are 110-113,116-164,167-172,174-184,186-189,191-193,195-208 and 211-218.

Continuation of Disposition of Claims: Claims rejected are 110,111,113,116-129,133-143,147-153,157-164,167-169,172,177-183,186-189,191-193,195-208 and 211-218.